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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,084	10/24/2001	Avi J. Ashkenazi	GNE.2630P1C66	4358

35489 7590 12/29/2005

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,084	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-65,68-70,74-77,86 and 87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *62-65,68-70 and 87* is/are allowed.

6)☒ Claim(s) *59-61, 74-77 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-58, 66-67, 71-73 and 78-85 are canceled.

Claims 61-62 and 74 have been amended.

2. Claims 59-65, 68-70, 74-77 and 86-87 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Objection.

Rejections Withdrawn

5. The rejection of claims 61-62 and 74-77 under 35 U.S.C. 112, second paragraph as being indefinite is withdrawn in view of the amendments to the claims.

6. The rejection of claims 58, 61-62 and 86-87 under 35 U.S.C 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicant' arguments and amendments to the claims.

7. The rejection of claims 62 and 87 under 35 U.S.C. 112, first paragraph, because the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention is withdrawn in view of applicant's arguments and upon further consideration.

Response to Arguments

8. The rejection of claims 59-60 and 74-77 under 35 U.S.C 112, first paragraph, as failing to comply with the written description requirement is maintained.

The response filed 10/5/2005 has been carefully considered, but is deemed not to be persuasive. Applicant reviews the evidentiary standard regarding the legal presumption of written description. The examiner takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of written description. The response argues that the present application discloses the native PRO337 sequence of SEQ ID NO:523 and the nucleic acid sequence of SEQ ID NO:522 which encodes it as well as methods for identifying proteins which are mitogens for inner ear supporting cells (see Example 116; pg. 347 of the specification). The response states that the specification further provides methods for determining the percent identity between two amino acid sequences and the specification provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity. Applicant's argument's have been fully considered, but are not found persuasive. Applicant's arguments appear to go more towards enablement, i.e., how to make and use, rather than the issue of adequate written description. Applicant is reminded that Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115) (see MPEP2161). Applicant argues that Skolnick et al is concerned with structural and functional predictions for unknown proteins and say nothing about the effects of amino

acid substitutions on the function of known proteins. In response to this argument, the claims are drawn to a genus of unknown proteins encoded by nucleic acids that have at least 85% sequence identity to the sequence of SEQ ID NO:522, which encodes the amino acid sequence of SEQ ID NO:523. Thus, Skolnick is directly on point, as Skolnick evinces that one cannot predict functional activity based on structural similarity, experimental research is necessary to confirm the artisan's best guess as to function. Applicant criticizes the art of Burgess and Lazar, stating that Burgess is limited to a non-conservative amino acid substitution at a residue already known to be important for activity and at amino acid residues known to be highly conserved in the entire EGF-like family of peptides and only two of the four substitutions resulted in any loss of activity. The response argues that there is no structural or functional similarity between PRO337 and the proteins of Burgess and Lazar and there is no basis for extrapolating the results obtained with these structurally different proteins to the predictability on the PRO337 sequence. In response to these arguments, it is important to note that the claims encompass polypeptides encoded by nucleic acids that are at least 85% identical to SEQ ID NO:522, which encompass polypeptides that are at best 85% identical to the protein of SEQ ID NO:523. Additionally, Applicant is holding the art to a higher standard than their own specification which does not disclose a single species having less than 100% nucleic acid sequence identity to SEQ ID NO:522 that encode a polypeptide that is a mitogen for inner ear supporting cells. The specification does not disclose the common features or attributes (structural domains) that are essential for activity (i.e., well conserved) and those that are non-essential within the genus. The art of Skolnick,

Burgess and Lazar evince that protein chemistry and assigning function to unknown proteins based upon structurally similarity is inaccurate and indicates that ordinary artisans could not predict the operability in the invention of the claimed genus from the written description of the present application. Again, the disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]. " See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004) ("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).

For inventions in an unpredictable art, adequate written description of a genus, which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case, applicant has not even disclosed a single species encompassed by the highly variant genus nor is there disclosure of the common attributes or features (i.e., structural domains) that are essential for activity or those which are non-essential. See, e.g., Eli Lilly. Description of a representative

number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, first paragraph. See MPEP 2163 IIA3(a)(ii).

Applicant argues that the instant claims are analogous to the claims discussed in Example 14 of the written description training materials, in which written description was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular activity, even though applicant had not made any variants. Applicant's arguments have been fully considered, however, unlike Example 14, the rejected claims do not require that the encoded polypeptide have at least 95% sequence identity with SEQ ID NO:523 and is a mitogen for inner ear supporting cells.

For these reasons the rejection is maintained.

9. The rejection of claims 59-61, 74-77 and 86 under 35 U.S.C. 112, first paragraph, because the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention is maintained.

The response argues that Example 116 (pg. 347 of spec.) provides step-by step guidelines and protocols for the proliferation of rat utricular supporting cells assay and one skilled in the art could easily test whether a variant PRO337 polypeptide is a

mitogen for inner ear supporting cells. Further, the response argues that the specification describes methods for the determination of percent identity and detailed guidance as to changes that may be made without adversely affecting PRO337 activity, including a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (page 180-183 and Table 6, page 182 of the specification). This has been fully considered, but is not found persuasive. Applicant's arguments essentially invite the skilled artisan to engage in experimentation to determine which of the 344 amino acids of the polypeptide of SEQ ID NO:523 are tolerant or intolerant to change using any of the twenty naturally occurring amino acid, and determine which of the innumerable combinations of amino acids substitutions are likely to be successful. To put this in perspective, the number of possible variant polypeptide sequences having 85% amino acid sequence identity to SEQ ID NO:523 (i.e., 52 amino acid substitutions of the 344 amino acid long polypeptide) is 20^{52} (approx. 4.5×10^{67}). Even for variant amino acid sequences having 95% amino acid sequence identity to SEQ ID NO:523, the number of sequences is 20^{17} (approx. $.1.3 \times 10^{22}$). Thus, Applicant's arguments to support the enablement of the claimed invention, is by invitation to the skilled artisan to design, construct, synthesize, isolate and screen the billions of polypeptide variants embraced by the broad scope of the claims where the guidance and direction to assist the skilled artisan in such an endeavor is limited and general in nature, suggesting exemplary substitutions, and various methods for making the modifications (i.e., site-directed mutagenesis, alanine scanning, ect).

In short, the instant application describes a method for determining whether a given polynucleotide encodes a polypeptide that possesses certain desired characteristics (i.e., mitogen for inner ear supporting cells), and identifies some broad categories of variants that *might work*, these descriptions, without more precise guidelines, amount to little more than "a starting point, a direction for further research." *Genentech*, 108 F.3d at 1366. *See also Calgene*, 188 F.3d at 1374 ("the teachings set forth in the specification provide no more than a 'plan' or 'invitation' for those of skill in the art to experiment practicing [the claimed invention]; they do not provide sufficient guidance or specificity as to how to execute that plan"); *National Recovery Technologies*, 166 F.3d at 1198 (stating that patent-in-suit "recognizes a specific need... and suggests a theoretical answer to that need. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement"). The instant specification does not describe the claimed invention in terms that will "enable any person skilled in the art... to make and use" the invention commensurate in scope with the claims. At most, the specification will enable a person of ordinary skill in the art to attempt to discover how to practice the claimed invention.

The response states that there is no requirement that the specification provide examples of making and using the claimed variant sequences having the claimed specificity. In response to this argument, the examiner acknowledges that enablement does not turn on the absence of a working example, however, as pointed out in the

rejection, the lack of a working example is a factor (i.e., Wands factor) to be considered, especially in a case involving an unpredictable art. See MPEP 2164.02.

Applicant criticizes the art of Ngo et al, stating that Ngo is concerned with structural and functional predictions for unknown proteins and say nothing about the effects of amino acid substitutions on the function of known proteins. In response to this argument, Applicant is again holding the art to a higher standard than their own application, which does not teach the effects of amino acid substitutions on PRO337 (SEQ ID NO:523). Additionally, Ngo is directly on point teaching that predictions of protein structure from the amino acid sequence alone is unpredictable, and thus, the encompassed variant sequences as having the same structure and function as the native PRO337 polypeptide cannot be predicted. Applicant argues that Wells et al teach that most mutations have small effects and large changes in function will often require mutation of more than one functional residue. In response to this argument, the claims encompass large changes in more than one functional residue and applicant has provided no guidance or direction as to PRO337 functional residues. Again, Applicant leaves this to the skilled artisan to decipher. Applicant argues that Bowie et al confirm that "proteins are surprisingly tolerant of amino acid substitution" (citing page 1306, column 2). In response to this argument, when Bowie is read in context, it is clear that the phrase is directed towards amino acid substitutions at positions that play little or no role in structure or function. Further, Bowie states "At other positions, no substitutions or only conservative substitutions were allowed." (page 1306, column 2). Again, one skilled in the art could not extrapolate the activity of PRO337 to the full scope of the

claimed polypeptide variants because the instant application does not provide any particular guidance or direction to assist the skilled artisan in making and using the polypeptide variants, the specification does not simplify the sequence space through identification of key residues, nor identify important structural and functional regions of PRO337.

The response argues that the claims are not directed towards all possible variants, but only those variants, which retain the function of the polypeptide as a mitogen for inner ear supporting cells. While it is true the claims are directed to only those polypeptide variants that have the functional activity of PRO337, Applicant has not provided any guidance or direction to assist the skilled artisan in making and using polypeptide variants that actually retain the function of PRO337 and the skilled artisan would have to design, construct, synthesize, isolate and screen the billions of polypeptide variants embraced by the broad scope of the claims to determine such. Applicant has not provided any evidence that it is routine, predictable and well within the realm of the skilled artisan to engage in experimentation of this magnitude sufficient to satisfy the first paragraph of 35 U.S.C. 112.

Due to the large quantity of experimentation necessary to generate the indefinite number of protein variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, which are tolerant to change, the absence of working examples directed to the same, the complex nature of the invention, the state of the art (Bowie et al, Wells and Ngo et al) which establishes the

unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

For these reasons the rejection is maintained

New Grounds of Objection

10. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Consider using the following title: "PRO337 Nucleic Acids".

Conclusions

11. Claims 62-65, 68-70 and 87 are in condition for allowance. The prior art does not teach or fairly suggest the recited sequences.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

SHEELA HUFF
PRIMARY EXAMINER